(19)日本国特許庁（ＪＰ）　(12)特　許　公　報（Ｂ２）　(11)特許番号
特許第3193262号
(P3193262)

(45)発行日　平成13年７月30日(2001.7.30)　(24)登録日　平成13年５月25日(2001.5.25)

(51)Int.Cl.⁷		識別記号	FI		
Ａ６１Ｍ	1/14	５６７	Ａ６１Ｍ	1/14	５６７
	1/18	５００		1/18	５００
Ｂ０１Ｄ	63/04		Ｂ０１Ｄ	63/04	
	65/02	５００		65/02	５００
// Ｄ０１Ｄ	5/24		Ｄ０１Ｄ	5/24	Ｚ

請求項の数６(全　５　頁)

(21)出願番号　特願平7－114514

(22)出願日　平成７年５月12日(1995.5.12)

(65)公開番号　特開平8－299433

(43)公開日　平成８年11月19日(1996.11.19)

審査請求日　平成10年７月９日(1998.7.9)

(73)特許権者　000003001
帝人株式会社
大阪府大阪市中央区南本町１丁目６番７号

(72)発明者　福原　聡
山口県岩国市日の出町２番１号　帝人株式会社　岩国事業所内

(72)発明者　江見　慎悟
山口県岩国市日の出町２番１号　帝人株式会社　岩国事業所内

(74)代理人　100077263
弁理士　前田　鈍博

審査官　稲村　正義

最終頁に続く

(54)【発明の名称】　血液処理器の製造方法及び血液処理器

1

(57)【特許請求の範囲】

【請求項１】　中空繊維半透膜型血液処理器の製造方法において、該中空繊維半透膜に塩化ナトリウム、無機リン酸塩及び保護剤を付着させ、且つ実質的に乾燥状態とした該中空繊維半透膜の集束体を筒状容器に装填し、末端を樹脂によりシール固定した後、少なくとも一端を切断して該中空繊維半透膜の中空部を開口させ、ヘッダー部材を取り付けることによって血液処理器を組み立て、該血液処理器内を実質的に乾燥状態に保持した状態で放射線滅菌することを特徴とする中空繊維半透膜型血液処理器の製造方法。

【請求項２】　該中空繊維半透膜が酢化度２０％以上のセルロースアセテートからなるものである請求項１記載の中空繊維半透膜型血液処理器の製造方法。

【請求項３】　塩化ナトリウム及び無機リン酸塩の総付着量が中空繊維半透膜のみの乾燥重量に対して0.1～2.0重量％であり、且つ塩化ナトリウム及び無機リン酸塩の組成比（重量比）が50：50～95：５である請求項１又は２記載の中空繊維半透膜型血液処理器の製造方法。

2

【請求項４】　中空繊維半透膜型血液処理器において、該中空繊維半透膜に塩化ナトリウム、無機リン酸塩及び保護剤が付着し、塩化ナトリウム及び無機リン酸塩の総付着量が中空繊維半透膜のみの乾燥重量に対して0.1～2.0重量％であり、且つ塩化ナトリウム及び無機リン酸塩の組成比（重量比）が50：50～95：５である中空繊維半透膜型血液処理器。

【請求項５】　該中空繊維半透膜が酢化度２０％以上のセルロースアセテートからなるものである請求項４記載の中空繊維半透膜型血液処理器。

【請求項６】　放射線滅菌をした請求項４又は５記載の

中空繊維半透膜型血液処理器。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は、血液透析、血液濾過、血漿分離などの血液処理に用いられる滅菌された中空繊維半透膜型血液処理器の製造方法に関する。

【０００２】

【従来技術】中空繊維半透膜型血液処理器の滅菌方法の一つとして放射線滅菌法がある。放射線滅菌を用いた場合、放射線による膜素材の分解、劣化が生じることが問題となる。例えば膜素材がセルロースアセテートの場合、放射線によるセルロースアセテートの分解が生じやすいため、グリセリンなどで保護したセルロースアセテート中空繊維半透膜を実質的に乾燥状態で放射線照射した後、蒸留水で抽出すると、抽出した水溶液は酸性を示す。従って、セルロースアセテート中空繊維半透膜からなり、実質的に乾燥状態で放射線照射滅菌を行った血液処理器を使用前に生理食塩水でプライミングした場合その液は酸性を示し、洗浄が不十分であれば酸性のプライミング液が体内に入る危険性があり、その対策が必要である。例えば特開平２－８８０７４号公報には中空繊維半透膜に保護剤（可塑剤）と共に緩衝剤を付着させ、実質的に乾燥状態でγ線照射滅菌する方法が開示されている。この方法により、放射線照射後の抽出液が酸性になるのを抑えることが可能となっている。

【０００３】しかしながら、該方法ではセルロースアセテート中空繊維半透膜に緩衝剤及びグリセリンなどの保護剤を付着させる工程で、緩衝剤及びグリセリンなどの保護剤を含む溶液のｐＨがアルカリ性を呈し、該工程においてセルロースアセテートの分解及び膜劣化を生じるとともに、その一部がセルロースに変換されて酢化度の低下を引き起こし、膜の表面電荷の変化によるタンパク質などの膜透過性能の低下が起こり、好ましくない。

【０００４】

【発明が解決しようとする課題】本願発明は、第一に従来の血液処理器製造上の問題点である中空繊維半透膜への保護剤の付着工程での分解及び膜劣化を防止し、更に放射線滅菌工程後のプライミング液の酸性化、膜の分解及び劣化を防止し、血液処理器の性能を向上させることを目的とする。

【０００５】

【課題を解決するための手段】本発明者は、かかる従来の問題点を解消することを目的として鋭意検討した結果、中空繊維半透膜表面に緩衝剤及び保護剤の付着処理工程において該処理混合溶液がアルカリ性を呈していたものが、従来、この溶液のｐＨに何ら影響しないと考えられていた中性塩である塩化ナトリウムを添加することにより処理溶液のｐＨを低下させることを見出した。このことにより血液処理器用の筒状容器に装填する前の中空繊維において保護剤の付着処理と同時に塩化ナトリウム及び無機リン酸塩の付着処理を実施することにより、緩衝剤及びグリセリンなどの保護剤付着工程での中空繊維半透膜の素材であるセルロースアセテートの分解、膜劣化を抑制し、その指標である酢化度の低下を抑制することが出来ることを見出し、更に放射線滅菌処理工程において、実質的に乾燥状態を保持した状態で中空繊維半透膜に対して放射線滅菌を施すことが可能となり、膜劣化防止効果も併せ持つことを見出し、本発明に到達した。

【０００６】本発明は、滅菌された中空繊維半透膜型血液処理器の製造方法において、該中空繊維半透膜に塩化ナトリウム、無機リン酸塩及び保護剤を付着させ、且つ実質的に乾燥状態とした該中空繊維半透膜の集束体を筒状容器に装填し、末端を樹脂によりシール固定後、少なくとも一端を切断して該中空繊維半透膜の中空部を開口させ、ヘッダー部材を取り付けることによって血液処理器を組み立て、該血液処理器内を実質的に乾燥状態に保持した状態で放射線滅菌することを特徴とする中空繊維半透膜型血液処理器の製造方法を提供するものである。

【０００７】以下、本発明について更に詳細に説明する。

【０００８】本発明にかかる中空繊維半透膜は、γ線などの放射線照射により酸を発生する可能性のある素材からなるものであって、例えばセルロースエステル、ポリメチルメタアクリレートなどが挙げられる。本発明は特に酢化度２０％以上のセルロースアセテートからなる中空繊維半透膜の場合に有効であって、その中でも酢化度３０～６１％の範囲であれば放射線照射による性能低下が少なく、より有利に適用可能となる。ここで酢化度とはポリマー中に占める酢酸の結合量をその重量％で示したものであり、平均酢化度を意味する。

【０００９】本発明における無機リン酸塩は、目的を達成しうるものであれば特に限定されるものではなく、その具体例としてはリン酸１水素カルシウム、リン酸３カリウム、リン酸３ナトリウム、リン酸水素２カリウム、リン酸水素２ナトリウム、リン酸２水素カリウム、リン酸２水素ナトリウムなど、更にこれらの組み合わせによるものなどが挙げられる。これらのなかで特に好ましいものとしては、リン酸水素２ナトリウムが挙げられる。

【００１０】塩化ナトリウム及び無機リン酸塩の総付着量としては、中空繊維半透膜のみの乾燥重量に対して0.1～2.0重量％、特に0.1～1.5重量％が好ましい。かかる範囲においては、滅菌後の膜劣化防止効果が確実に得られるのと同時に、中空繊維半透膜とシール用樹脂の接着不良によるシール不良を防止しやすい利点がある。総付着量が2.0重量％を越えると、乾燥時に塩化ナトリウム及び無機リン酸塩が析出し、過剰に中空繊維半透膜表面に付着することにより樹脂によるシール固定が困難となる。逆に総付着量が0.1％未満では滅菌後の抽出液のｐＨが酸性になるのを防ぎ難い問題点を有する。

5

【００１１】塩化ナトリウム及び無機リン酸塩の組成比（重量比）としては、50：50～95：５、特に80：20～95：５の範囲が好ましい。かかる範囲では、滅菌後の抽出液のｐＨが酸性になるのを防止すると共に、中空繊維半透膜に塩化ナトリウム、無機リン酸塩及び保護剤を付着させる工程で、該混合溶液のｐＨがアルカリ性になるのを防止し易い利点がある。

【００１２】本発明における保護剤とは、中空繊維半透膜を実質的に乾燥状態にした時の膜の細孔の保護、透水性などの膜性能低下を防止する目的で付着させるものであり、グリセリン、ポリエチレングリコールなどの多価アルコールなどが好ましく、それらの中でも特にグリセリンが好ましい。かかる保護剤の中空繊維半透膜への付着量の適正範囲は半透膜の種類により異なり、その細孔空孔率の比較的低い透析膜から空孔率の高い血漿分離膜まで、その飽和付着量によって決定される。ここで膜内細孔部の全部が保護剤で置換、充填された状態が飽和付着状態であり、その時の保護剤付着量が飽和付着量である。本発明における保護剤の好ましい付着量は実質上飽和付着量未満であって、更に好ましくは中空繊維半透膜の乾燥重量に対して４０～３００重量%が好ましく、特に５０～２００重量%が好ましい。該付着量が４０重量%未満では放射線による膜劣化及び乾燥時の膜の透水性などの性能低下を回避することが困難な場合がある。また飽和付着量以上に保護剤を付着させると過剰の保護剤は中空繊維半透膜の中空内表面又は外表面に液滴状に点在し、中空繊維半透膜と樹脂とのシール固定が困難になることがある。それ故、保護剤付着量の好ましい範囲の上限として３００重量%が挙げられる。

【００１３】本発明において、中空繊維半透膜に塩化ナトリウム、無機リン酸塩及び保護剤を付着せしめ、且つ実質的に乾燥状態にする方法としては特に限定されるものではなく、例えば所定濃度の塩化ナトリウム、無機リン酸塩及び保護剤の混合水溶液を中空繊維半透膜に付着させ、余分の水溶液をエアナイフで取り除いた後、熱風中で十分に乾燥する方法が挙げられる。ここでいう実質的な乾燥状態とは、通常は菌が増殖しにくい程度に乾燥されていることを意味し、特に中空繊維半透膜の膜壁中の細孔内全体に水分が存在する状態に達しない量であることが菌の増殖防止を確実にしやすい点から望ましい。また中空繊維半透膜をコア剤を用いた湿式紡糸などの方法で製造する場合には、コア剤を洗浄した後で塩化ナトリウム、無機リン酸塩及び保護剤を付着せしめることが好ましい。

【００１４】本発明ではこのようにして得られた塩化ナトリウム、無機リン酸塩、及び保護剤を付着せしめ、且つ実質的に乾燥状態とした該中空繊維半透膜の集束体を血液処理器用の筒状容器に装填せしめ、ウレタン樹脂或いはエポキシ樹脂などの樹脂を用いて遠心成型などにより両端をシールした後、その少なくとも一端の中空繊維

6

半透膜を固定した樹脂とともに切断して中空繊維半透膜の中空部を開口させ、更にその開口部に血液などを分配するためのヘッダー部材を固着せしめることによって、血液処理器を組み立てる。本発明では、かかる血液処理器においてその内部を実質的に乾燥状態に保持したままでポリエチレン、ポリエステルなどの袋に入れて密封した後、γ線などの放射線を照射することによって滅菌処理を行う。放射線の照射量としては、中空繊維半透膜などの血液処理器を構成する部材に悪影響を与えないで滅菌効果が得られる範囲であればよく、１５～５０ｋＧｙの範囲が好ましい。

【００１５】

【実施例】以下に本発明の実施例を比較例と共に示すが、本発明はそれらによって限定されるものではない。

【００１６】［実施例１及び実施例２］

ー塩化ナトリウム、リン酸水素２ナトリウムの総付着量の検討ー

セルロースジアセテート（平均重合度：２６０、酢化度５３．８%）のフレークス、ポリエチレングリコール（平均分子量４００）、ジグリセリン、１，４ーブタンジオールからなる混合物を加熱溶融し、二重管ノズルの外管から押し出し、内管から芯材として窒素ガスを同時に吐出し、２００ｍ／分で巻き取り、内径２００μｍ、外径２３０μｍの中空繊維原膜を得た。この原膜を８０℃の温浴に３０秒間浸漬処理し、続いて塩化ナトリウム及びリン酸水素２ナトリウムの５５重量%グリセリン混合水溶液に１分間浸漬後、膜外表面に付着した過剰のグリセリンを圧空で除去、熱風で乾燥し、セルロースジアセテートの中空繊維半透膜を得た。この時、塩化ナトリウム及びリン酸水素２ナトリウムの水溶液の濃度を下表記載の如く変えることにより、乾燥後の中空繊維半透膜のみの重量に対する塩化ナトリウム及びリン酸水素２ナトリウムの総付着量を約１．０重量%（＝実施例１）及び約０．３重量%（＝実施例２）となるように調製した。この時の混合溶液のｐＨと膜劣化の指標であるセルロースジアセテートの酢化度を表１に示した。この中空繊維半透膜の半透膜を長さ２７ｃｍに切断したものを約１２，０００本束ね、ポリカーボネイト樹脂の筒状ケースに収納し乾燥した後、両端をポリウレタン樹脂で固定後切断し、さらにヘッダー部材を取り付け、血液透析器を組み立てた。その後、ポリエチレン袋に密封し、カートンケースに梱包した。この状態で２２ｋＧｙのγ線を照射し、滅菌処理を行った。照射後、中空繊維半透膜を約２ｃｍに切断したもの１．５ｇに蒸留水１５０mlを加え、７０℃、１時間加温し、試験液とする。該試験液及び使用した蒸留水それぞれ２０mlに１ｇ／Ｌの濃度の塩化カリウム水溶液を１ml加えた溶液のｐＨを測定し、両液のｐＨ差（ΔｐＨ）を算出した結果、表１の結果を得た。透析型人工腎臓装置承認基準ではこのΔｐＨが１．５未満であることが必要であり、１．５以上は血液処理

器としては好ましくない。

【００１７】この結果、塩化ナトリウム、リン酸水素２ナトリウム及びグリセリンの混合水溶液のｐＨが８付近となり、セルロースジアセテートの分解、膜劣化が抑え＊

＊られ、酢化度の減少が抑制された。またｐＨ差も基準内であった。

【００１８】

【表１】

	NaCl濃度（重量%）	Na_2HPO_4濃度（重量%）	NaCl・Na_2HPO_4総付着量（重量%）	混合水溶液ｐＨ(50℃)	酢化度	ΔｐＨ	備考
実施例１	0.87	0.13	1.04	8.19	53.51	1.03	
実施例２	0.261	0.039	0.28	8.13	53.46	1.32	
比較例１	0	0.3	0.28	8.73	52.00	1.22	
比較例２	0	0	0	6.84	53.68	1.66	
比較例３	0.087	0.013	0.06	8.16	53.53	1.50	
比較例４	2.01	0.30	2.34	8.17	53.50	0.39	ウレタン部の接着不良発生

【００１９】［比較例１］実施例１での５５重量%グリセリン混合水溶液浴でのセルロースジアセテート中空繊維半透膜を処理する工程で、リン酸水素２ナトリウム濃度が０．３%であるグリセリン水溶液浴で処理した結果、ΔｐＨは基準内であったが、酢化度が減少しており、セルロースジアセテートの分解、膜劣化が生じた。

【００２０】［比較例２］実施例１での５５重量%グリセリン混合水溶液浴でのセルロースジアセテート中空繊維半透膜を処理する工程で、塩化ナトリウム、リン酸水素２ナトリウムを共に含まないグリセリン水溶液浴で処理した結果、酢化度は原料のフレークスと変わらず、セルロースジアセテートの分解、膜劣化は起きないが、ΔｐＨは基準外の結果となった。

【００２１】［比較例３］実施例１の５５重量%グリセリン混合水溶液浴でセルロースジアセテート中空繊維半透膜を処理する工程で、塩化ナトリウム及びリン酸水素２ナトリウム総付着量が０．１重量%となるように塩化ナトリウム及びリン酸水素２ナトリウムの濃度を変え、血液処理器を得た。その結果、塩化ナトリウム及びリン酸水素２ナトリウム総付着量が本願特許請求の範囲よりも少なくてもセルロースジアセテートの分解、膜劣化は起こらないが、ΔｐＨが高く基準外であった。

【００２２】［比較例４］実施例１の５５重量%グリセリン混合水溶液浴でセルロースジアセテート中空繊維半透膜を処理する工程で、塩化ナトリウム及びリン酸水素２ナトリウム総付着量が２．３重量%となるように塩化ナトリウム及びリン酸水素２ナトリウムの濃度を変え、血液処理器を得た。その結果、塩化ナトリウム及びリン酸水素２ナトリウム添加の混合水溶液のｐＨは低下し、膜劣化は抑えられたが、ウレタン樹脂と中空繊維半透膜との接着不良が発生した。

【００２３】［実施例３］実施例１及び比較例１記載の血液処理器について、クリアランス測定を行い、表２の結果を得た。クリアランス測定は、血液側溶液としてデキストラン（平均分子量１万）の０．２g/L水溶液、あるいはα－ラクトアルブミン、ミオグロビン、チトクロー

9

ムＣの０．１g/Lリン酸緩衝溶液（NaCl 9g/L, Na_2HPO_4 3 7.7g/L, KH_2PO_4 7.9g/L）を用い、中空糸入口側流量を２００ml／分、出口側流量１９２ml／分で流した。それと同時に筒状ケース内に透析液の代わりにイオン交換水を５００ml／分で流した。測定は３７℃で実施した。クリアランス（C_L：ml/min）は次式により求めた。

【００２４】$C_L = (Q_{Bi} \times C_{Bi} - Q_{Bo} \times C_{Bo}) / C_{Bi}$

上式における略号は以下の通りである。

C_{Bi}：血液側溶液の入口側濃度（g/L）

C_{Bo}：血液側溶液の出口側濃度（g/L）

10

＊Q_{Bi}：血液側溶液の入口側流量（g/分）

Q_{Bo}：血液側溶液の出口側流量（g/分）

【００２５】結果、糖類であるデキストランのクリアランスは、実施例１及び比較例１記載の血液処理器において差は認められないが、タンパク質であるα－ラクトアルブミン、ミオグロビン、チトクロームＣのクリアランスは実施例１の血液処理器において大幅に向上した。

【００２６】

【表２】

＊10

	酢化度	クリアランス（ml／min）			
		ﾃﾞｷｽﾄﾗﾝ	α-ﾗｸﾄｱﾙﾌﾞﾐﾝ	ﾐｵｸﾞﾛﾋﾞﾝ	ﾁﾄｸﾛｰﾑC
実施例１	53.51	２１	４５	４２	３６
比較例１	52.00	２１	３８	３３	３０

【００２７】

【発明の効果】本発明の血液処理器の製造方法によれば、使用前に生理食塩水でプライミングした場合のプライミング液を無害化し、安全性に優れた血液処理器を提供することが出来る。またセルロースアセテートの分解、膜劣化を防ぎ、酢化度を高く保持できるため、膜の表面電荷の変化に伴うタンパク質の膜透過性能の低下を防ぐことが出来る。更には滅菌前における血液処理器内での菌の増殖を防ぎ、パイロジェンのない血液処理器が容易に得られる。

※

フロントページの続き

(56)参考文献　特開　平２－88074（ＪＰ，Ａ）
特開　平４－33657（ＪＰ，Ａ）
特開　平２－268767（ＪＰ，Ａ）
特開　昭62－74364（ＪＰ，Ａ）
特開　平５－192397（ＪＰ，Ａ）

(58)調査した分野(Int.Cl.[7]，ＤＢ名)
A61M　1/14　567
A61M　1/18　500
B01D　63/04
B01D　65/02　500
D01D　5/24

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 08-299433
(43)Date of publication of application : 19.11.1996

(51)Int.Cl. A61M 1/14
A61K 35/14
A61M 1/18
B01D 63/04
B01D 65/02
// D01D 5/24

(21)Application number : 07-114514
(22)Date of filing : 12.05.1995

(71)Applicant : TEIJIN LTD
(72)Inventor : FUKUHARA SATOSHI
EMI SHINGO

(54) METHOD FOR PREPARING BLOOD PROCESSING DEVICE AND THE BLOOD PROCESSING DEVICE

(57)Abstract:
PURPOSE: To prevent a film from being deteriorated in the manufacturing process of a hollow fiber semipermeable membrane-type blood processing device and to provide a method for manufacturing a high performance blood processing device.
CONSTITUTION: By adhering the hollow fiber semipermeable membrane of a hollow fiber semipermeable membrane-type blood processing device with sodium chloride, an inorg. phosphate and a protective agent, it is possible to prevent a film from being deteriorated in a protective agent applying process and a radiation beam sterilizing process.

LEGAL STATUS

[Date of request for examination]	09.07.1998
[Date of sending the examiner's decision of rejection]	
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]	
[Date of final disposal for application]	
[Patent number]	3193262
[Date of registration]	25.05.2001
[Number of appeal against examiner's decision of rejection]	
[Date of requesting appeal against examiner's decision of rejection]	
[Date of extinction of right]	

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] In the manufacture approach of a hollow fiber semipermeable membrane mold blood treater to this hollow fiber semipermeable membrane A sodium chloride, Make an inorganic-phosphoric-acid salt and a protective agent adhere, and a tubed container is loaded with the focusing object of this hollow fiber semipermeable membrane substantially made into dryness. After carrying out seal immobilization of the end with resin, cut an end at least and opening of the centrum of this hollow fiber semipermeable membrane is carried out. The manufacture approach of the hollow fiber semipermeable membrane mold blood treater characterized by carrying out radappertization where it assembled the blood treater and the inside of this blood treater is substantially held to dryness by attaching header material.
[Claim 2] The manufacture approach of the hollow fiber semipermeable membrane mold blood treater according to claim 1 which is what this hollow fiber semipermeable membrane becomes from 20% or more of cellulose acetate whenever [acetylation].
[Claim 3] The manufacture approach of a hollow fiber semipermeable membrane mold blood treater according to claim 1 or 2 that the total coating weight of a sodium chloride and an inorganic-phosphoric-acid salt is 0.1 - 2.0 % of the weight to the dry weight of only hollow fiber semipermeable membrane, and the presentation ratios (weight ratio) of a sodium chloride and an inorganic-phosphoric-acid salt are 50:50-95:5.
[Claim 4] The hollow fiber semipermeable membrane mold blood treater whose presentation ratios (weight ratio) of a sodium chloride and an inorganic-phosphoric-acid salt a sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent adhere to this hollow fiber semipermeable membrane, and the total coating weight of a sodium chloride and an inorganic-phosphoric-acid salt is 0.1 - 2.0 % of the weight to the dry weight of only hollow fiber semipermeable membrane in a hollow fiber semipermeable membrane mold blood treater, and are 50:50-95:5.
[Claim 5] The hollow fiber semipermeable membrane mold blood treater according to claim 4 which is what this hollow fiber semipermeable membrane becomes from 20% or more of cellulose acetate whenever [acetylation].
[Claim 6] The hollow fiber semipermeable membrane mold blood treater according to claim 4 or 5 which carried out radappertization.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the manufacture approach of the sterilized hollow fiber semipermeable membrane mold blood treater which is used for blood processing of hemodialysis, hemofiltration, plasma skimming, etc.
[0002]
[Description of the Prior Art] There is radiation sterilization as one of the sterilization approaches of a hollow fiber semipermeable membrane mold blood treater. When radappertization is used, that disassembly of the film material by the radiation and degradation arise poses a problem. For example, as for the extracted water solution, acidity is shown, when a film material is cellulose acetate and distilled water extracts, after carrying out radiation irradiation of the cellulose acetate hollow fiber semipermeable membrane which protected with the glycerol etc. by dryness substantially since it is easy to produce decomposition of the cellulose acetate by the radiation. Therefore, it consists of cellulose acetate hollow fiber semipermeable membrane, when a priming is carried out with a physiological saline before using the blood treater which performed radiation irradiation sterilization by dryness substantially, the liquid shows acidity and has the danger that acid priming liquid will go into the inside of the body if washing is inadequate, and the cure is required. For example, a buffer is made for JP,2-88074,A to adhere to hollow fiber semipermeable membrane with a protective agent (plasticizer), and the approach of carrying out gamma irradiation sterilization by dryness substantially is indicated. It is possible to stop that the extract after radiation irradiation becomes acidity by this approach.
[0003] However, while pH of the solution containing protective agents, such as a buffer and a glycerol, presents alkalinity and produces decomposition and film degradation of cellulose acetate in this process at the process which makes protective agents, such as a buffer and a glycerol, adhere to cellulose acetate hollow fiber semipermeable membrane by this approach, the part is changed into a cellulose, the fall of whenever [acetylation] is caused, the fall of membrane permeability ability, such as protein by change of membranous surface charge, takes place, and it is not desirable.
[0004]
[Problem(s) to be Solved by the Invention] The invention in this application prevents decomposition at an adhesion process and film degradation of the protective agent to the hollow fiber semipermeable membrane which is a trouble on the conventional blood treater manufacture in the first place, prevents decomposition and degradation of souring of the priming liquid after a radappertization process and the film further, and aims at raising the engine performance of a blood treater.
[0005]
[Means for Solving the Problem] this invention person found out reducing pH of a processing solution by adding the sodium chloride whose thing to which this processing mixed solution was presenting alkalinity to the hollow fiber semipermeable membrane front face in adhesion down stream processing of a buffer and a protective agent is the neutral salt considered not to influence pH of this solution at all conventionally, as a result of inquiring wholeheartedly for the purpose of canceling this conventional trouble. By carrying out adhesion processing of a sodium chloride and an inorganic-phosphoric-acid salt to adhesion processing of a protective agent and coincidence in the hollow fiber before loading the

tubed container for blood treaters by this Decomposition of the cellulose acetate which is the material of the hollow fiber semipermeable membrane in protective agent adhesion processes, such as a buffer and a glycerol, Find out that film degradation can be controlled and the fall of whenever [acetylation / which is the index] can be controlled, and it is further set to radappertization down stream processing. It became possible to give radappertization to hollow fiber semipermeable membrane, where dryness is held substantially, and a header and this invention were reached [also having the film degradation prevention effectiveness and].

[0006] In the manufacture approach of a hollow fiber semipermeable membrane mold blood treater that this invention was sterilized A sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent are made to adhere to this hollow fiber semipermeable membrane. And a tubed container is loaded with the focusing object of this hollow fiber semipermeable membrane substantially made into dryness. Resin cuts an end for an end at least after seal immobilization, and opening of the centrum of this hollow fiber semipermeable membrane is carried out. By attaching header material, a blood treater is assembled and the manufacture approach of the hollow fiber semipermeable membrane mold blood treater characterized by carrying out radappertization where the inside of this blood treater is substantially held to dryness is offered.

[0007] Hereafter, this invention is further explained to a detail.

[0008] The hollow fiber semipermeable membrane concerning this invention consists of a material which may generate an acid by radiation irradiation, such as a gamma ray, and cellulose ester, polymethylmethacrylate, etc. are mentioned. In the case of the hollow fiber semipermeable membrane which consists of 20% or more of cellulose acetate whenever [acetylation], especially this invention is effective, and if it is 30 - 61% of range whenever [acetylation] also in it, there will be little degradation by radiation irradiation and it will become more advantageously applicable. Whenever [acetylation] shows the amount of association of the acetic acid occupied in a polymer by the weight %, and means whenever [average acetylation] here.

[0009] The inorganic-phosphoric-acid salt in this invention is not limited especially if the purpose can be attained, and as the example, things further depended on such combination, such as calcium hydrogenphosphate monobasic, tribasic potassium phosphate, phosphoric-acid 3 sodium, dibasic potassium phosphate, disodium hydrogen-phosphate, potassium dihydrogen phosphate, and sodium dihydrogen phosphate, are mentioned. As a desirable thing, disodium hydrogen-phosphate is especially mentioned in these.

[0010] As the total coating weight of a sodium chloride and an inorganic-phosphoric-acid salt, 0.1 - 1.5 % of the weight is especially desirable 0.1 to 2.0% of the weight to the dry weight of only hollow fiber semipermeable membrane. In this range, there is an advantage which is easy to prevent the poor seal depended on that the film degradation prevention effectiveness after sterilization is acquired certainly and coincidence badly [adhesion of hollow fiber semipermeable membrane and the resin for seals]. If the total coating weight exceeds 2.0 % of the weight, a sodium chloride and an inorganic-phosphoric-acid salt will deposit at the time of desiccation, and the seal immobilization by resin will become difficult by adhering to a hollow fiber semipermeable membrane front face superfluously. Conversely, the total coating weight has the trouble which cannot prevent pH of the extract after sterilization becoming acidity easily at less than 0.1%.

[0011] As a presentation ratio (weight ratio) of a sodium chloride and an inorganic-phosphoric-acid salt, the range of 50:50-95:5, especially 80:20-95:5 is desirable. In this range, while preventing that pH of the extract after sterilization becomes acidity, there is an advantage which is easy to prevent that pH of this mixed solution becomes alkalinity at the process which makes a sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent adhere to hollow fiber semipermeable membrane.

[0012] The protective agent in this invention is made to adhere in order to prevent membraneous ability falls, such as protection of the pore of the film when making hollow fiber semipermeable membrane into dryness substantially, and water permeability, its polyhydric alcohol, such as a glycerol and a polyethylene glycol, etc. is desirable, and its glycerol is desirable also especially in them. The proper range of the coating weight to the hollow fiber semipermeable membrane of this protective agent changes with classes of semipermeable membrane, and is determined by the saturation coating weight from the comparatively low permeable membrane of the pore void content to a plasma

demarcation membrane with a high void content. The condition of having permuted and filled up with all of the pore sections in the film here with the protective agent is in a saturation adhesion condition, and the protective agent coating weight at that time is saturation coating weight. It is under saturation-on parenchyma coating weight, the desirable coating weight of the protective agent in this invention has 40 - 300 still more preferably desirable % of the weight to the dry weight of hollow fiber semipermeable membrane, and its 50 - 200 % of the weight is especially desirable. It may be difficult for this coating weight to avoid degradation of the film at the time of film degradation by the radiation, and desiccation, such as water permeability, at less than 40 % of the weight. Moreover, when a protective agent is made to adhere more than saturation coating weight, the hollow internal surface or outside surface of hollow fiber semipermeable membrane may be dotted with a superfluous protective agent liquid drop-like, and seal immobilization with hollow fiber semipermeable membrane and resin may become difficult. So, 300 % of the weight is mentioned as an upper limit of the range where protective agent coating weight is desirable.

[0013] In this invention, after making a sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent adhere to hollow fiber semipermeable membrane, and not being limited especially as an approach of making it into dryness substantially, and making the sodium chloride of predetermined concentration, an inorganic-phosphoric-acid salt, and the mixed water solution of a protective agent adhere to hollow fiber semipermeable membrane, for example, removing an excessive water solution with an air knife, the approach of fully drying in hot blast is mentioned. It is desirable from the point that it tends to ensure growth prevention of a bacillus that it is the amount which does not reach the condition that substantial dryness here means that extent which a bacillus cannot usually increase easily is dry, and moisture exists in [of an in / the membranous wall of hollow fiber semipermeable membrane / whole] pore especially. Moreover, when manufacturing hollow fiber semipermeable membrane by approaches, such as wet spinning using a core agent, after washing a core agent, it is desirable to make a sodium chloride, an inorganic-phosphoric-acid salt, and a protective agent adhere.

[0014] The sodium chloride, inorganic-phosphoric-acid salt which were obtained by doing in this way in this invention, And make a protective agent adhere and the tubed container for blood treaters is made to load with the focusing object of this hollow fiber semipermeable membrane substantially made into dryness. After carrying out the seal of the both ends by centrifugal molding etc. using resin, such as urethane resin or an epoxy resin, A blood treater is assembled by cutting with the resin which fixed the hollow fiber semipermeable membrane of an end at least, carrying out opening of the centrum of hollow fiber semipermeable membrane, and making the header material for distributing blood etc. to the opening further fix. In this invention, after putting into bags, such as polyethylene and polyester, and sealing, holding the interior to dryness substantially in this blood treater, sterilization processing is performed by irradiating radiations, such as a gamma ray. The range of 15-50kGy is [that what is necessary is just the range where the sterilization effectiveness is acquired without having a bad influence on the member which constitutes blood treaters, such as hollow fiber semipermeable membrane, as an exposure of a radiation] desirable.

[0015]

[Example] This invention is not limited by them although the example of this invention is shown with the example of a comparison below.

[0016] [An example 1 and an example 2]

- Heating fusion of the mixture which consists of the flakes of the examination-cellulose diacetate (average degree of polymerization: whenever [260 and acetylation] 53.8%) of the total coating weight of a sodium chloride and disodium hydrogen-phosphate, a polyethylene glycol (mean molecular weight 400), diglycerol, and 1,4-butanediol was carried out, it extruded from the outer tube of a double pipe nozzle, nitrogen gas was rolled round from the inner tube by part for discharge and 200m/to coincidence as a core material, and the hollow fiber original film with a bore [of 200 micrometers] and an outer diameter of 230 micrometers was obtained. The superfluous glycerol which carried out immersion processing of this original film for 30 seconds at the 80-degree C hot bath, and adhered to the 55-% of the weight glycerol mixed water solution of a sodium chloride and disodium hydrogen-phosphate after immersion for 1 minute continuously at the film outside surface was dried by removal and hot blast by the compressed air, and the hollow fiber semipermeable membrane of cellulose diacetate was obtained. At this time, by changing the concentration of the water solution of a sodium

chloride and disodium hydrogen-phosphate like a following table publication, the total coating weight of the sodium chloride and disodium hydrogen-phosphate to the weight of only the hollow fiber semipermeable membrane after desiccation was prepared so that it might become about 1.0 % of the weight (= example 1) and about 0.3 % of the weight (= example 2). Whenever [acetylation / of the cellulose diacetate which is pH of the mixed solution at this time and the index of film degradation] was shown in Table 1. After containing what cut the semipermeable membrane of this hollow fiber semipermeable membrane in die length of 27cm in the tubed case of polycarbonate resin in the about 12,000 bundle and drying, polyurethane resin cut both ends after immobilization, header material was attached further, and the hemodialyzer was assembled. Then, it sealed into the polyethylene bag and packed up in the carton case. The gamma ray of 22kG(ies) was irradiated in this condition, and sterilization processing was performed. 150ml of distilled water is added to 1.5g of things which cut hollow fiber semipermeable membrane to about 2cm after an exposure, and it warms for 1 hour and let 70 degrees C be test fluid. As a result of measuring pH of the solution which added 1ml of potassium chloride water solutions of the concentration of 1 g/L to this test fluid and 20ml of each used distilled water and computing pH difference (deltapH) of both liquid, the result of Table 1 was obtained. On dialysis mold hemodialysis apparatus acknowledgement criteria, it is required for this deltapH to be less than 1.5, and 1.5 or more are not desirable as a blood treater.

[0017] Consequently, pH of a sodium chloride, disodium hydrogen-phosphate, and the mixed water solution of a glycerol became the eight neighborhoods, decomposition of cellulose diacetate and film degradation were suppressed, and reduction which is whenever [acetylation] was controlled. Moreover, pH difference was also in criteria.

[0018]

[Table 1]

	NaCl濃度（重量%）	Na_2HPO_4濃度（重量%）	NaCl・Na_2HPO_4総付着量（重量%）	混合水溶液pH(50℃)	酢化度	ΔpH	備考
実施例1	0.87	0.13	1.04	8.19	53.51	1.03	
実施例2	0.261	0.039	0.28	8.13	53.46	1.32	
比較例1	0	0.3	0.28	8.73	52.00	1.22	
比較例2	0	0	0	6.84	53.68	1.66	
比較例3	0.087	0.013	0.06	8.16	53.53	1.50	
比較例4	2.01	0.30	2.34	8.17	53.50	0.39	ウレタン部の接着不良発生

[0019] Although deltapH was in criteria as a result of processing by the glycerol water-solution bath whose disodium hydrogen-phosphate concentration is 0.3% at the process which processes the cellulose-diacetate hollow fiber semipermeable membrane in the 55-% of the weight glycerol mixed water solution bath in the [example 1 of comparison] example 1, whenever [acetylation] was decreasing and decomposition of cellulose diacetate and film degradation arose.
[0020] Although whenever [acetylation] was not different from the flakes of a raw material and decomposition of cellulose diacetate and film degradation did not break out at the process which processes the cellulose-diacetate hollow fiber semipermeable membrane in the 55-% of the weight glycerol mixed water solution bath in the [example 2 of comparison] example 1 as a result of processing by the glycerol water-solution bath containing neither a sodium chloride nor disodium hydrogen-phosphate, deltapH brought a result besides criteria.
[0021] At the process which processes cellulose-diacetate hollow fiber semipermeable membrane by the 55-% of the weight glycerol mixed water solution bath of the [example 3 of comparison] example 1, the concentration of a sodium chloride and disodium hydrogen-phosphate was changed so that the sodium chloride and disodium hydrogen-phosphate total coating weight might become 0.1 % of the weight, and the blood treater was obtained. consequently, the sodium chloride and disodium hydrogen-phosphate total coating weight -- this application -- although decomposition of cellulose diacetate and film degradation at least did not take place rather than a claim, deltapH was outside criteria highly.

[0022] At the process which processes cellulose-diacetate hollow fiber semipermeable membrane by the 55-% of the weight glycerol mixed water solution bath of the [example 4 of comparison] example 1, the concentration of a sodium chloride and disodium hydrogen-phosphate was changed so that the sodium chloride and disodium hydrogen-phosphate total coating weight might become 2.3 % of the weight, and the blood treater was obtained. Consequently, although pH of a sodium chloride and the mixed water solution of disodium hydrogen-phosphate addition fell and film degradation was suppressed, the adhesive agent of urethane resin and hollow fiber semipermeable membrane occurred.
[0023] About the blood treater of [example 3] example 1 and example of comparison 1 publication, path clearance measurement was performed and the result of Table 2 was obtained. Path clearance measurement passed the amount of hollow filament inlet-port side streams by part for part [for /], and 200ml outlet side flow rate/of 192ml, using 0.2 g/L water solution of a dextran (mean molecular weight 10,000) or alpha-lactalbumin, a myoglobin, and the 0.1 g/L phosphoric-acid buffer solution (NaCl 9 g/L, Na2HPO4 37.7 g/L, KH2PO4 7.9 g/L) of Cytochrome C as a blood side solution. Ion exchange water was poured by part for 500ml/instead of dialysing fluid in the tubed case to it and coincidence. Measurement was carried out at 37 degrees C. It asked for path clearance (CL:ml/min) by the degree type.
[0024] The cable address in a CL=(QBixCBi-QBoxCBo)/CBi top type is as follows.
CBi: Entrance-side concentration of a blood side solution (g/L)
CBo: Outlet side concentration of a blood side solution (g/L)
QBi: The amount of inlet-port side streams of a blood side solution (a part for g/)
QBo: The outlet side flow rate of a blood side solution (a part for g/)
[0025] The path clearance of alpha-lactalbumin whose path clearance of the dextran which are a result and a saccharide is protein although a difference is not accepted in the blood treater of example 1 and example of comparison 1 publication, a myoglobin, and Cytochrome C improved sharply in the blood treater of an example 1.
[0026]
[Table 2]

	酢化度	クリアランス (ml/min)			
		ﾃﾞｷｽﾄﾗﾝ	α-ﾗｸﾄｱﾙﾌﾞﾐﾝ	ﾐｵｸﾞﾛﾋﾞﾝ	ﾁﾄｸﾛｰﾑC
実施例1	53.51	21	45	42	36
比較例1	52.00	21	38	33	30

[0027]
[Effect of the Invention] According to the manufacture approach of the blood treater of this invention, the priming liquid at the time of carrying out a priming with a physiological saline before use can be defanged, and the blood treater excellent in safety can be offered. Moreover, since decomposition of cellulose acetate and film degradation are prevented and whenever [acetylation] can be held highly, the fall of the membrane permeability ability of the protein accompanying change of membranous surface charge can be prevented. Furthermore, growth of the bacillus within the blood treater before sterilization is prevented, and a blood treater without a pyrogen is obtained easily.

[Translation done.]